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# Enantiodivergent Approach to the Synthesis of *cis*-2,6-Disubstituted Piperidin-4-ones

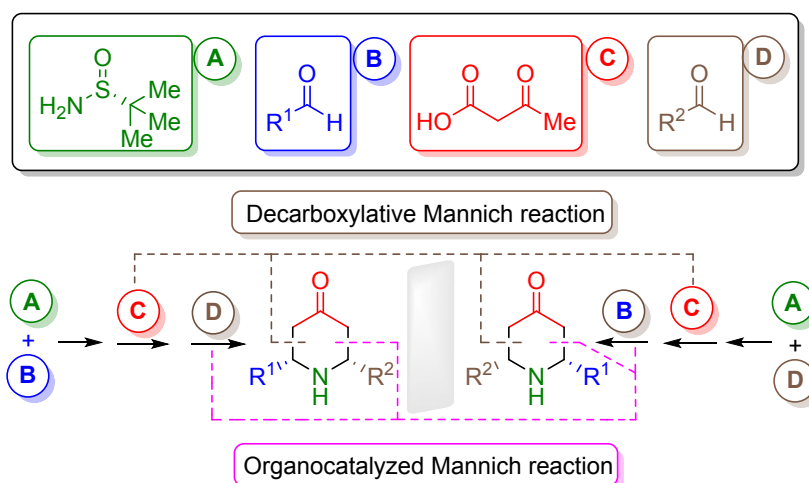
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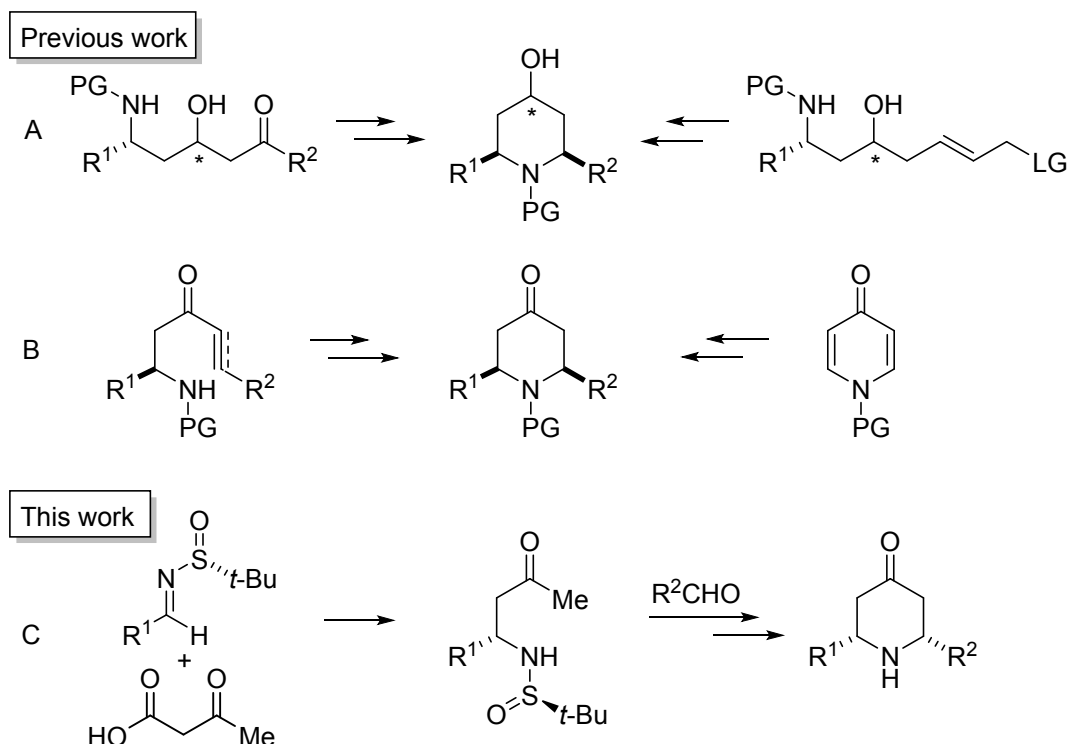


**ABSTRACT.** Enantiopure  $\beta$ -amino ketone derivatives were synthesized by decarboxylative Mannich reaction of chiral *N*-*tert*-butanesulfinyl imines with  $\beta$ -keto acids, and were subsequently transformed into *cis*-2,6-disubstituted piperidin-4-ones through an organocatalyzed condensation with aldehydes. Both enantiomers were accessible from the same precursors by inverting the order in the reaction sequence of the aldehydes involved in the imine formation and the intramolecular Mannich condensation. The synthesis of the piperidine alkaloids (+)-241D, (–)-epimyrtine and (–)-lasubine II demonstrated the utility of this methodology.

**KEYWORDS.** Chiral sulfinyl imines,  $\beta$ -amino ketones, diastereoselective Mannich reactions, enantioselective synthesis, piperidine alkaloids.

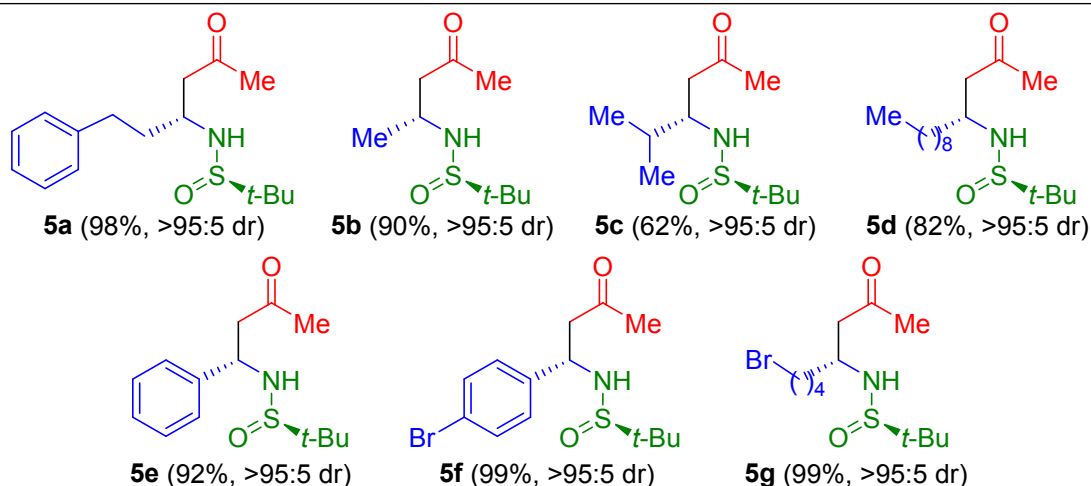
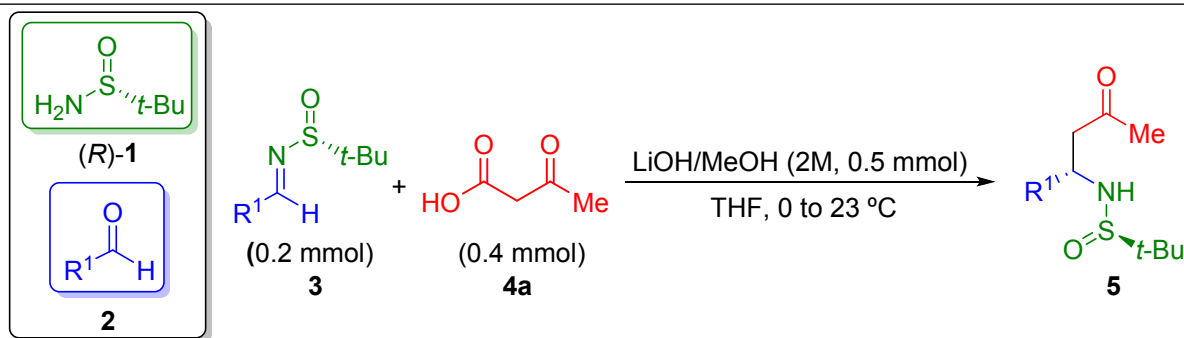
## INTRODUCTION

Piperidine moiety is commonly found in natural alkaloids, pharmaceuticals and other compounds which exhibit a broad range of biological activities.<sup>1</sup> Particularly, systems with the piperidin skeleton having substituents at 2- and 6-positions with a relative *cis*-configuration, and a carbonyl or a hydroxyl group at 4-position are of special interest. Consequently, the asymmetric synthesis of these polysubstituted piperidine derivatives has attracted much attention that is reflected in the development of numerous strategies on that purpose.<sup>2</sup> The most general methods involve as key steps of the synthesis of these compounds either an intramolecular condensation follow by reduction from the corresponding amino ketone derivative<sup>3</sup> or an intramolecular allylic substitution,<sup>4</sup> as depicted in Scheme 1A. Access to piperidin-4-one derivatives was also possible by intramolecular conjugate addition in  $\alpha,\beta$ -unsaturated amino ketones,<sup>5</sup> or by double conjugate addition to *N*-protected pyridine-4(1*H*)-ones<sup>6</sup> (Scheme 1B). Although some of these methods work efficiently, long reaction sequences and the use of expensive reagents and ligands to control the stereochemistry are important drawbacks that should be mentioned. Due to that, new general, simple and efficient methods to prepare *cis*-2,6-disubstituted piperidin-4-ones in an enantioselective fashion are highly desirable. For that reason, we envisaged a new strategy in which a sequential decarboxylative Mannich reaction of a chiral *N*-*tert*-butanesulfinyl imine and a  $\beta$ -keto acid,<sup>7</sup> followed by an organocatalyzed intramolecular Mannich reaction involving an aldehyde<sup>8</sup> would produce the substituted piperidines in a straightforward manner, comprising this methodology three synthetic operations (imine formation and two consecutive Mannich reactions) from readily available starting materials (Scheme 1C).

**Scheme 1.** Previous work and our methodology for the synthesis of substituted piperidines

## RESULTS AND DISCUSSION

We commenced our study with chiral  $\beta$ -amino ketone derivatives **5**. We had already described the stereoselective synthesis of these compounds in a previous communication, by coupling of 3-oxobutanoic acid (**4a**) and *N*-*tert*-butanesulfinyl imines **3** under basic conditions,<sup>7</sup> except **5b** which is a new compound. The decarboxylative Mannich reaction proceeded with high yields and excellent diastereoselectivities (Table 1). In addition, the starting chiral imines **3**,<sup>9</sup> which have been extensively used as electrophiles in synthesis over the past decade, were easily accessible by condensation of aldehydes **2** and (*R*)-*tert*-butanesulfinamide [(*R*)-**1**] in the presence of titanium tetraethoxide.<sup>10</sup> Regarding the configuration of the newly created stereogenic center, we observed that the nucleophilic attack took always place to the *Si*-face of imines **3** with *R*<sub>S</sub> configuration.<sup>7</sup>

**Table 1.** Decarboxylative Mannich-type coupling of imines **3** and 3-oxobutanoic acid (**4a**)<sup>a</sup>

<sup>a</sup> Isolated yields after column chromatography purification are given in parentheses. Diastereomeric ratios were determined by <sup>1</sup>H NMR analysis of crude reaction mixture.

With enantiopure  $\beta$ -amino ketone derivatives **5** in hand, we focused then on the development of reaction conditions to perform an intramolecular Mannich condensation involving a second aldehyde. We took compound **5a** derived from 3-phenylpropanal (**2a**) as a model compound, and inspired by the work of Rutjes and co-workers,<sup>8</sup> the amine hydrochloride **6a**, resulting from the removal of the *tert*-butanesulfinyl group under acidic reaction conditions, was treated with 1 equivalent of triethylamine, magnesium sulfate and benzaldehyde (**2e**) in ethanol, in the presence of 20 mol% of racemic proline, at room temperature for 5 hours. The expected 2,6-disubstituted piperidin-4-one **7a** was obtained in 60% isolated yield (Table 2, entry 1). The intramolecular condensation did not work in the absence of proline or triethyl amine (Table 2, entries 2 and 3). On the other hand, the condensation proceeded only in 39% if pyrrolidine was used instead of proline as organocatalyst (Table 2, entry 4). It seems that the amino acid functionality was beneficial for this transformation. However, yield was even lower when the reaction was performed in the presence of sarcosine, the simplest acyclic secondary  $\beta$ -amino acid (22%, Table 2, entry 5). Remarkably, working with enantiopure proline, the desired compound **7a** was formed in more than 75% yield (Table 2, entries 6 and 7). Concerning the configuration of the new stereocenter, compound **7a** was always isolated with relative *cis* configuration, independently of the configuration of the organocatalyst (Table 2, entries 1, 6 and 7). That means that the stereochemical

outcome is governed exclusively by the stereocenter already present in compound **6** and not by the organocatalyst.

**Table 2.** Optimization of the reaction conditions for 2,6-disubstituted piperidin-4-ones **7** formation

Entry	Reaction conditions	Yield (%) <sup>a</sup>
1	D/L-Proline (20 mol%), Et <sub>3</sub> N (1 equiv), MgSO <sub>4</sub> (1 equiv), EtOH, rt, 5 h	60
2	Et <sub>3</sub> N (1 equiv), MgSO <sub>4</sub> (1 equiv), EtOH, rt, 5 h	--
3	D/L-Proline (20 mol%), MgSO <sub>4</sub> (1 equiv), EtOH, rt, 5 h	--
4	Pyrrolidine (20 mol%), Et <sub>3</sub> N (1 equiv), MgSO <sub>4</sub> (1 equiv), EtOH, rt, 5 h	39
5	Sarcosine (20 mol%), Et <sub>3</sub> N (1 equiv), MgSO <sub>4</sub> (1 equiv), EtOH, rt, 5 h	22
6	D-Proline (20 mol%), Et <sub>3</sub> N (1 equiv), MgSO <sub>4</sub> (1 equiv), EtOH, rt, 5 h	75
7	L-Proline (20 mol%), Et <sub>3</sub> N (1 equiv), MgSO <sub>4</sub> (1 equiv), EtOH, rt, 5 h	77

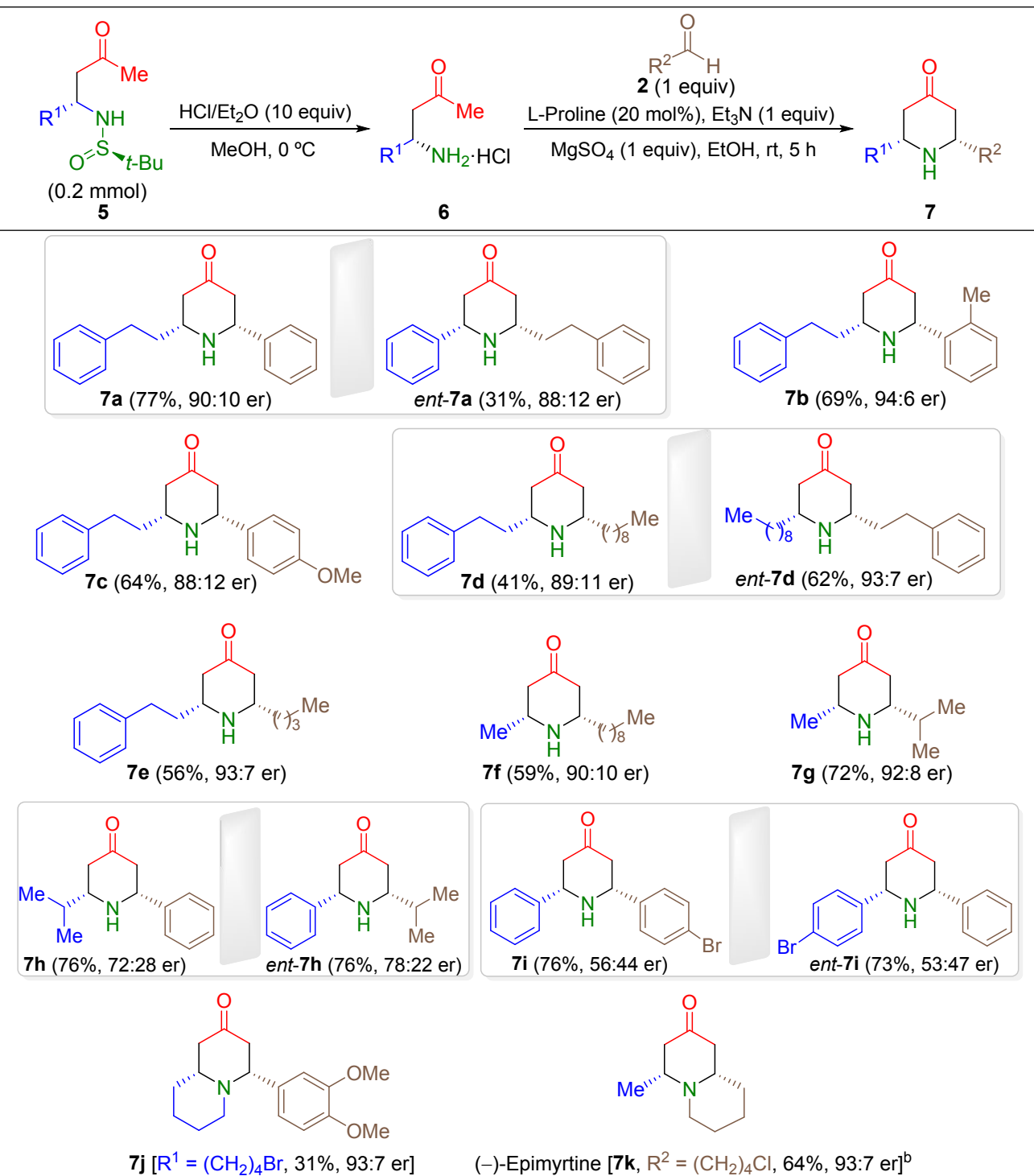
<sup>a</sup> Isolated yields after column chromatography purification based on the starting β-amino ketone derivative **5a**.

Proline

Sarcosine

We studied next the scope of the intramolecular Mannich reaction involving β-amino ketone derivatives **5** and different aldehydes **2**, by applying the optimized conditions shown in Table 2, entry 7, and using L-proline, which is by far the most economical stereoisomer of proline, as organocatalyst. The relative configuration was determined to be *cis* by NOESY experiments in 2,6-disubstituted piperidin-4-ones **7**, which were obtained in relatively good to moderate yields (Table 3). As a general rule, enolizable aldehydes **2** provided lower yields than aromatic aldehydes. It merits mention that this methodology allows access to the quinolizidine moiety when starting from the appropriate precursors. For instance, the reaction of compound **5g** derived from the imine of 5-bromopentanal (**2g**) with veratraldehyde (3,4-dimethoxybenzaldehyde, **2k**) led to quinolizidinone derivative **7j** in only 31% yield, meanwhile, the reaction of **5b** with 5-chloropentanal (**2l**) gave rise to natural product (–)-epimyrine<sup>11</sup> (**7k**), isolated from bilberry (*Vaccinium Myrtillus*)<sup>12</sup> (Table 3). In both cases, after formation of the piperidine ring through the expected Mannich condensation, a subsequent intramolecular *N*-alkylation involving the carbon-halogen bond occurred<sup>13</sup> to produce the quinolizidinic systems. The relatively low yield for quinolizidine **7j** could be explained considering the competition between intramolecular *N*-alkylation and imine formation previous to the intramolecular Mannich condensation. Thus, if intramolecular *N*-alkylation involving highly

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2 reactive carbon-bromine bond takes place first, subsequent intramolecular Mannich condensation  
3 does not occur. Importantly, it is possible through this methodology to synthesize two enantiomeric  
4 piperidines **7** starting from the same precursors. For instance, (*R*)-*tert*-butanesulfinamide [(*R*)-**1**], 3-  
5 phenylpropanal (**2a**), benzaldehyde (**2e**) and 3-oxobutanoic acid (**4a**) were the common starting  
6 materials in the synthesis of **7a** and *ent*-**7a**. This could be considered a kind of enantiodivergent<sup>14</sup>  
7 approach to 2,6-disubstituted piperidines **7**. Moreover, the order in the reaction sequence involving  
8 aldehydes **2** determines the configuration of the two possible enantiomers. In the same way, **7d** and  
9 *ent*-**7d** were prepared from 3-phenylpropanal (**2a**) and decanal (**2d**), **7h** and *ent*-**7h** from  
10 isobutyraldehyde (**2c**) and benzaldehyde (**2e**), and piperidines **7i** and *ent*-**7i** from benzaldehyde (**2e**)  
11 and *p*-bromobenzaldehyde (**2f**) (Table 3). Regarding the absolute configuration of *cis* 2,6-  
12 disubstituted piperidin-4-ones **7**, the stereochemical integrity of these compounds was determined  
13 by chiral HPLC and GC analysis. Relatively high enantiomeric ratios were observed for compounds  
14 wearing alkyl substituents at 2 and 6 positions, meanwhile almost racemic mixtures were formed in  
15 the case of diaryl substituted piperidinones (**7i** and *ent*-**7i**) in the organocatalyzed cyclization step  
16 (Table 3).  
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**Table 3.** Synthesis of 2,6-disubstituted piperidin-4-ones **7** from  $\beta$ -amino ketone derivatives **5**<sup>a</sup>

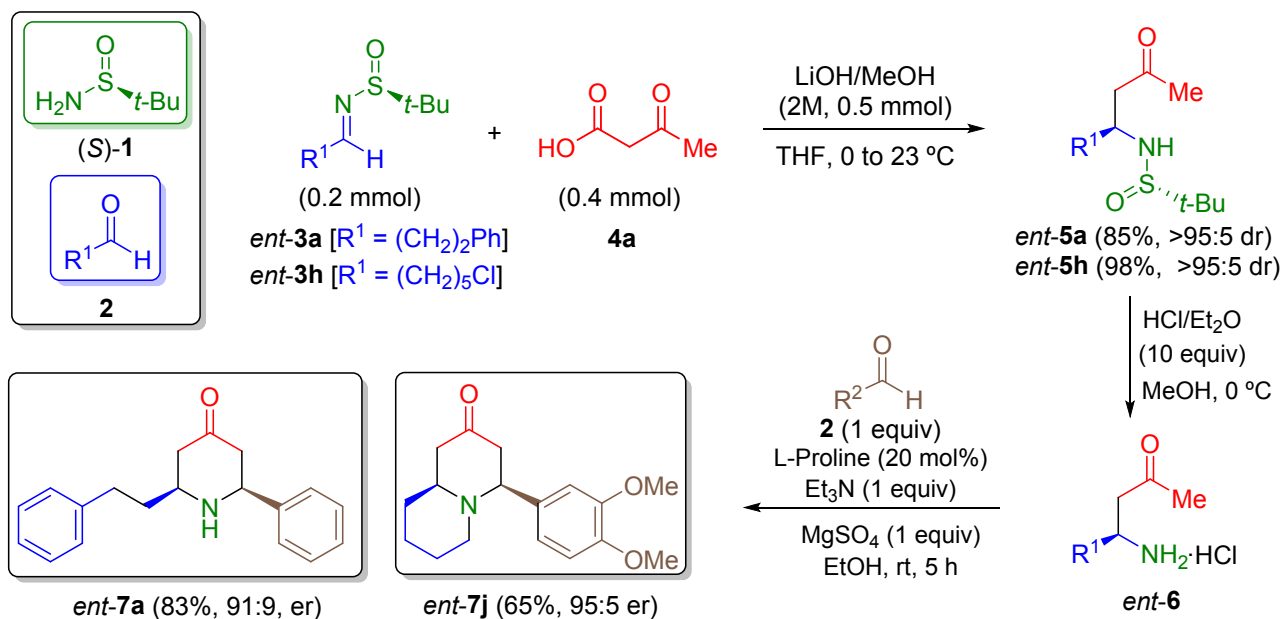
<sup>a</sup> Isolated yields after column chromatography purification are given in parentheses and are based on the starting  $\beta$ -amino ketone derivative **5**. <sup>b</sup> Isolated as the corresponding hydrochloride derivative.

Enantiomeric piperidines *ent-7* were also obtained working with sulfonamide (*S*)-**1** (through the looking glass) under the optimized reaction conditions, as depicted on Scheme 2. Thus, compounds *ent-7a* and *ent-7j* were prepared starting from chiral imines *ent-3a* and *ent-3h*, respectively. The organocatalyzed intramolecular Mannich condensation is the key step to be considered in the election of the best strategy for the synthesis of both enantiomers. For instance, *ent-7a* was obtained from *ent-5a* by condensation with benzaldehyde (**2e**) in 83% (Scheme 2). However, condensation of

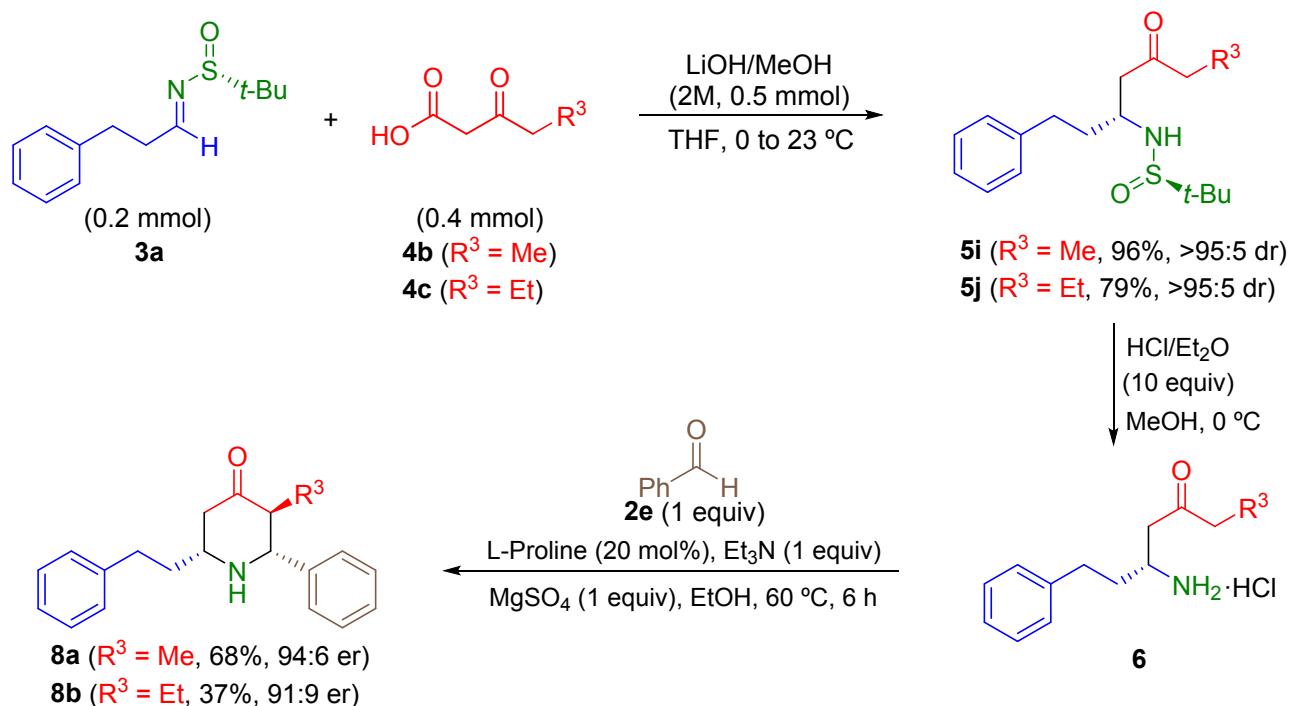


**5e** with enolizable 3-phenylpropanal (**2a**) proceeded in a poor 31% yield to give the same stereoisomer *ent-7a* (Table 3).

**Scheme 2.** Synthesis of 2,6-disubstituted piperidin-4-ones **7** starting from sulfonamide (*S*)-**1**

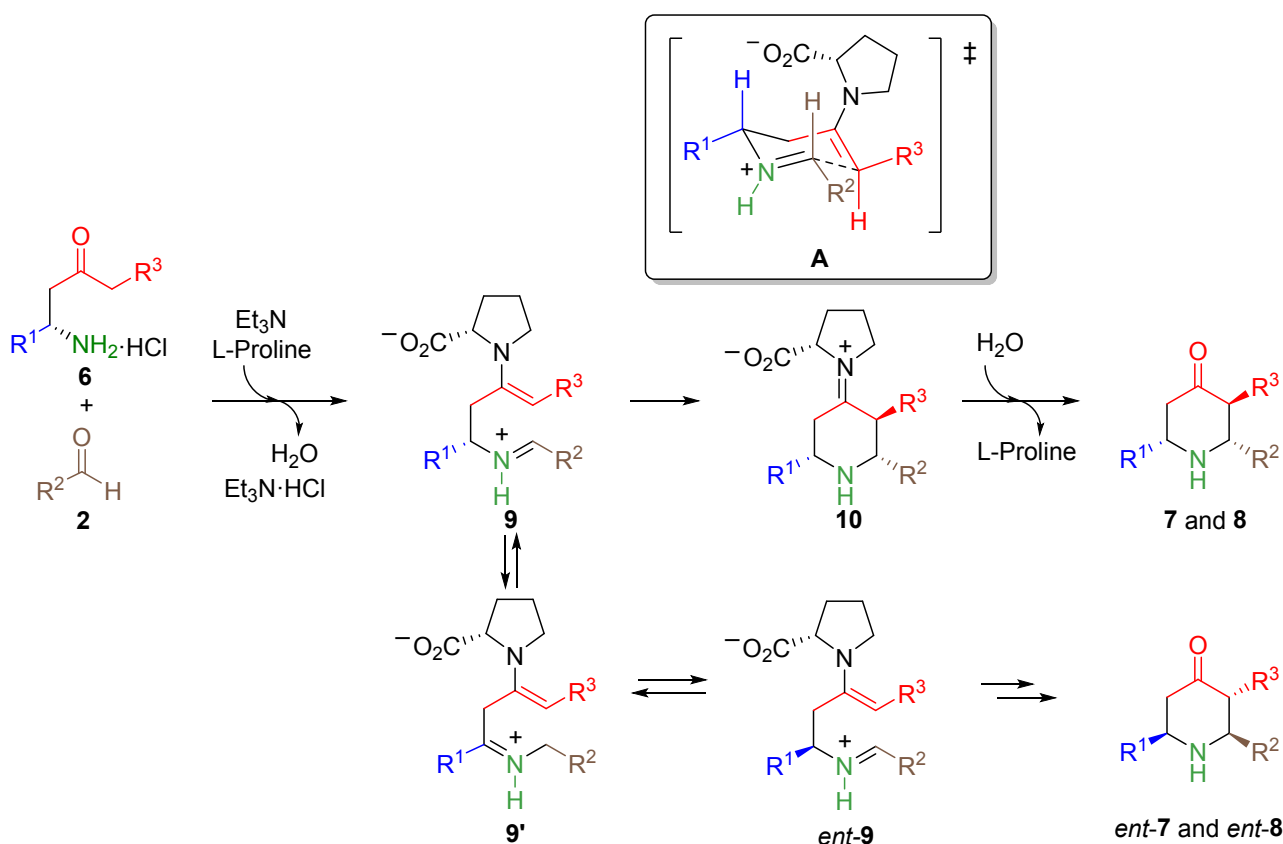


We explored also the  $\beta$ -keto acid **4** scope with chiral imine **3a** under the optimized reaction conditions. The decarboxylative Mannich condensation with 3-oxopentanoic acid (**4b**) and 3-oxohexanoic acid (**4c**) leading to compounds **5i** and **5j** took place in 96 and 79% yield, respectively (Scheme 3). Unfortunately, the subsequent organocatalyzed intramolecular Mannich condensation proceeded in low yield at room temperature. Pleasingly, we found that the expected 2,3,6-trisubstituted piperidin-4-ones **8** were obtained in reasonable yields by performing the reaction at 60 °C for 6 h. In addition, compounds **8** displayed almost exclusively 2,6-*cis*-2,3-*trans* relative configuration (Scheme 3).

**Scheme 3.** Synthesis of 2,3,6-trisubstituted piperidin-4-ones **8**

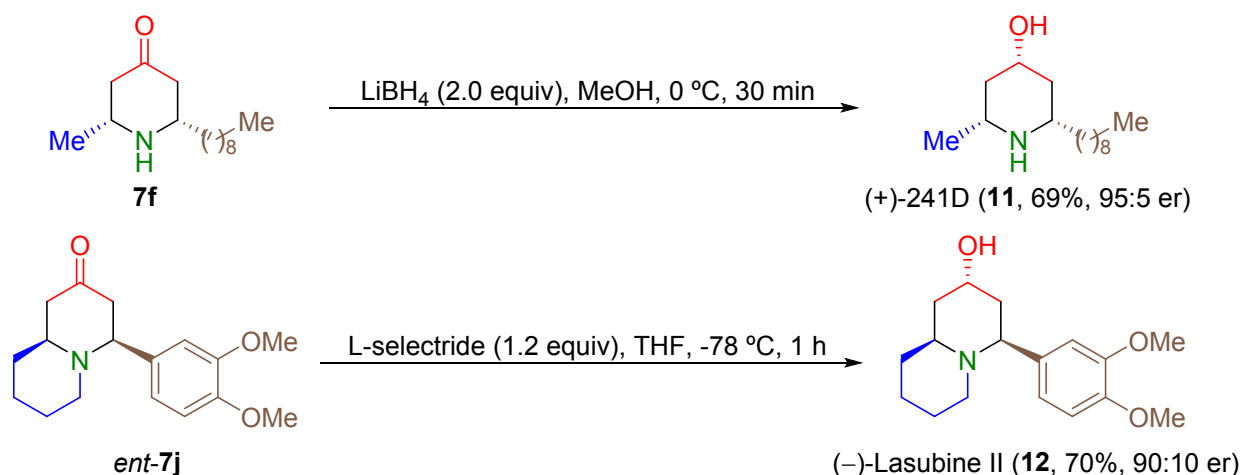
A mechanism has been proposed in order to rationalize the stereochemical outcome. Thus, the cyclization proceeded in an iminium-enamine intermediate **9** which is formed by double condensation involving on one side the aldehyde **2** and the primary amine group of compounds **6**, and on the other side L-proline and the ketone functionality of **6**.<sup>8</sup> The nucleophilic attack of the enamine moiety to the iminium took place through a Zimmerman-Traxler six-membered transition state **A**, with the bulky  $R^1$ ,  $R^2$  and  $R^3$  groups placed in equatorial positions in a chair-like conformation, in order to minimized destabilizing steric interactions. The resulting cyclic iminium compounds **10** was further hydrolyzed to yield the expected piperidin-4-ones **7** and **8**, releasing L-proline, which would be prone to participate in a new cyclization process. Formation of the corresponding enantiomers *ent-7* and *ent-8* could be explained by considering that isomerization of iminium **9** to give **9'** could take place in some extension, being facilitated the process when  $R^1$  and  $R^2$  are aromatic rings. In this isomerization occurs, the stereochemical integrity is not maintained at the stereogenic center of compounds **6** (Scheme 4).

**Scheme 4.** Rationalization of the stereochemical outcome of the organocatalyzed intramolecular Mannich reaction



In addition to natural product (–)-epimyrtime (**7k**), enantiomerically pure piperidin-4-ones **7** could be also interesting precursors of alkaloids with potential biological activity. For instance, compounds **7f** and *ent*-**7j** were transformed into natural alkaloids (+)-241D<sup>4a,5b,11g,15</sup> (**11**) and (–)-lasubine II<sup>16</sup> (**12**), respectively, by stereoselective reduction of the carbonyl group. Thus, alkaloid (+)-241D (**11**), isolated from the methanolic skin extracts of the Panamanian poison frog *Dendrobates speciosus*,<sup>17</sup> was synthesized by reduction of **7f** with lithium borohydride<sup>18</sup> in MeOH at 0 °C, in 69% yield after column chromatography purification, as a single stereoisomer (Scheme 5). Opposite relative facial-selectivity was observed in the reduction of compound *ent*-**7j** with L-selectride<sup>19</sup> at low temperature, leading in this case to (–)-lasubine II (**12**) in 70% yield, a natural product isolated from plants of the *Lythraceae* family<sup>20</sup> (Scheme 5).

**Scheme 5.** Synthesis of (+)-241D (**11**) and (–)-lasubine II (**12**) from piperidin-4-ones **7f** and *ent*-**7j**, respectively



## CONCLUSIONS

We have developed a methodology for the enantioselective synthesis of *cis*-2,6-disubstituted piperidin-4-ones. Decarboxylative Mannich reaction of a chiral *N*-*tert*-butanesulfinyl imine with a  $\beta$ -keto acid, followed by a L-proline organocatalyzed intramolecular Mannich reaction of the resulting  $\beta$ -amino ketone derivative with an aldehyde, allowed access to either enantiomer of the possible disubstituted piperidinones using the same precursors, including the chiral auxiliary. The configuration of the reaction products is determined by order of the reactions of carbonyl compounds **2** involved in the formation of the chiral imine **3** and in the intramolecular organocatalyzed condensation. Finally, the straightforward synthesis of alkaloids (+)-241D, (–)-epimyrine and (–)-lasubine II demonstrated the potential in synthesis of this procedure.

## EXPERIMENTAL SECTION

**General Remarks:** *tert*-Butanesulfinamides **1** (*R* and *S*) were a gift of Medalschmery (> 99% ee by chiral HPLC on a Chiracel AS column, 90:10 *n*-hexane/*i*-PrOH, 1.2 mL/min,  $\lambda$ =222 nm). TLC was performed on silica gel 60 F<sub>254</sub>, using aluminum plates and visualized with phosphomolybdic acid and potassium permanganate stain. Flash chromatography was carried out on handpacked columns of silica gel 60 (230–400 mesh). Melting points are uncorrected. Optical rotations were measured using a polarimeter with a thermally jacketted 5 cm cell at approximately 20 °C and concentrations (*c*) are given in g/100 mL. Infrared analyses were performed with a spectrophotometer equipped with an ATR component; wavenumbers are given in cm<sup>–1</sup>. Low-resolution mass spectra (EI) were obtained at 70 eV; and fragment ions in *m/z* with relative intensities (%) in parentheses. High-resolution mass spectra (HRMS) were also carried out in the electron impact mode (EI) at 70 eV

using a quadrupole mass analyzer or in the electrospray ionization mode (ESI) using a TOF analyzer. NMR Spectra were recorded at 300 or 400 MHz for  $^1\text{H}$  NMR and 75 or 100 MHz for  $^{13}\text{C}$  NMR, using  $\text{CDCl}_3$  as the solvent, and TMS as internal standard (0.00 ppm). The data are being reported as: s = singlet, d = doublet, t = triplet, q = quadruplet, m = multiplet or unresolved, br s = broad signal, coupling constant(s) in Hz, integration.  $^{13}\text{C}$  NMR spectra were recorded with  $^1\text{H}$ -decoupling at 100 MHz and referenced to  $\text{CDCl}_3$  at 77.16 ppm. DEPT-135 experiments were performed to assign  $\text{CH}$ ,  $\text{CH}_2$  and  $\text{CH}_3$ . Compounds **3a**, *ent*-**3a** [ $\text{R}^1 = \text{Ph}(\text{CH}_2)_2$ ],<sup>21</sup> **3b** ( $\text{R}^1 = \text{Me}$ ),<sup>22</sup> **3c** ( $\text{R}^1 = i\text{-Pr}$ ),<sup>10</sup> **3d** [ $\text{R}^1 = \text{Me}(\text{CH}_2)_8$ ],<sup>23</sup> **3e** ( $\text{R}^1 = \text{Ph}$ ),<sup>10</sup> **3f** ( $\text{R}^1 = 4\text{-BrC}_6\text{H}_4$ ),<sup>24</sup> **3g** [ $\text{R}^1 = \text{Br}(\text{CH}_2)_4$ ]<sup>25</sup> and *ent*-**3h** [ $\text{R}^1 = \text{Cl}(\text{CH}_2)_4$ ]<sup>26</sup> were prepared from the corresponding aldehyde and (*R*)- or (*S*)-*tert*-butanesulfinamide **1** in THF, in the presence of two equivalents of titanium tetraethoxide. Compounds **4a-c** were prepared by hydrolysis of the corresponding commercially available  $\beta$ -keto ester.

### General Procedure for the Reaction of $\beta$ -Keto Acids **4** with *N*-*tert*-Butanesulfinyl Imines **3**.

**Synthesis of Compounds 5:** These compounds were prepared by the previously published method in reference 7. Yields, physical and spectroscopic data for new compounds **5** follow.

**(4*R*,*R*<sub>S</sub>)-4-Amino-*N*-(*tert*-butanesulfinyl)pentan-2-one (5b):** The representative procedure was followed by using  $\beta$ -keto acid **4a** (81.6 mg, 0.8 mmol) and imine **3b** (59.0 mg, 0.4 mmol). Purification by column chromatography (hexane/AcOEt, 1:2) yielded **5a** (74.0 mg, 0.36 mmol, 90%) as a yellow liquid;  $[\alpha]_{\text{D}}^{20} -93.7$  ( $c = 1.03$ ;  $\text{CH}_2\text{Cl}_2$ );  $R_f$  0.10 (hexane/EtOAc, 1:3); IR  $\nu$  (neat) 3220, 2966, 2872, 1710, 1457, 1410, 1363, 1172, 1044, 796  $\text{cm}^{-1}$ ;  $^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ )  $\delta$  4.07 (d,  $J = 6.6$  Hz, 1H), 3.74–3.70 (m,  $J = 6.5$  Hz, 1H), 2.78 (dd,  $J = 17.6, 5.4$  Hz, 1H), 2.69 (dd,  $J = 17.6, 6.0$  Hz, 1H), 2.13 (s, 3H), 1.22 (d,  $J = 6.6$  Hz, 3H), 1.16 (s, 9H);  $^{13}\text{C}\{^1\text{H}\}$  NMR (100 MHz,  $\text{CDCl}_3$ )  $\delta$  207.8 (C), 55.4 (C), 50.6 ( $\text{CH}_2$ ), 48.1 (CH), 30.8 (CH), 22.5 ( $\text{CH}_3$ ), 21.4 ( $\text{CH}_3$ ); LRMS (EI)  $m/z$  205 ( $\text{M}^+$ , 2%), 149 (11), 111 (13), 91 (36), 85 (9), 70 (16), 61 (14), 57 (32), 45 (15), 44 (10), 43 (100), 42 (10), 41 (14); HRMS (ESI)  $m/z$  ( $\text{M} - \text{C}_4\text{H}_8$ )<sup>+</sup> calcd for  $\text{C}_5\text{H}_{11}\text{NO}_2\text{S}$  149.0510, found 149.0515.

**(4*S*,*S*<sub>S</sub>)-4-Amino-8-chloro-*N*-(*tert*-butanesulfinyl)octan-2-one (*ent*-**5h**):** The representative procedure was followed by using  $\beta$ -keto acid **4a** (81.6 mg, 0.8 mmol) and imine *ent*-**3h** (107.2 mg, 0.4 mmol). Purification by column chromatography (hexane/AcOEt, 1:2) yielded *ent*-**5h** (137.7 mg, 0.392 mmol, 98%) as a colorless oil;  $[\alpha]_{\text{D}}^{20} +45.9$  ( $c = 1.09$ ,  $\text{CH}_2\text{Cl}_2$ );  $R_f$  0.19 (hexane/EtOAc, 1:3); IR  $\nu$  (neat) 2955, 1710, 1457, 1411, 1363, 1169, 1048, 899, 734  $\text{cm}^{-1}$ ;  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  4.01 (d,  $J = 9.1$  Hz, 1H), 3.54 (t,  $J = 6.5$  Hz, 3H), 2.92 (dd,  $J = 17.9, 5.6$  Hz, 1H), 2.81 (dd,  $J = 17.9, 4.6$  Hz, 1H), 2.16 (s, 3H), 1.84–1.71 (m, 2H), 1.69–1.41 (m, 4H), 1.21 (s, 9H);  $^{13}\text{C}\{^1\text{H}\}$  NMR

(100 MHz, CDCl<sub>3</sub>)  $\delta$  208.1 (C), 55.9 (C), 53.5 (CH), 49.0 (CH<sub>2</sub>), 44.8 (CH<sub>2</sub>), 34.7 (CH<sub>2</sub>), 32.0 (CH<sub>2</sub>), 31.0 (CH), 23.4 (CH<sub>2</sub>), 22.6 (CH<sub>3</sub>); LRMS (EI)  $m/z$  225 (M<sup>+</sup> – C<sub>4</sub>H<sub>8</sub>, 12%), 169 (36), 167 (100), 161 (8), 57 (35), 43 (35), 41 (11); HRMS (EI)  $m/z$  (M – C<sub>4</sub>H<sub>8</sub>)<sup>+</sup> calcd for C<sub>8</sub>H<sub>16</sub>ClNO<sub>2</sub>S 225.0590, found 225.0593.

**(6*R*,8*S*)-6-Amino-*N*-(*tert*-butanesulfinyl)-8-phenyloctan-4-one (5j):** The representative procedure was followed by using  $\beta$ -keto acid **4c** (52.0 mg, 0.4 mmol) and imine **3a** (48 mg, 0.2 mmol). Purification by column chromatography (hexane/AcOEt, 1:2) yielded **5j** (51.3 mg, 0.158 mmol, 79%) as a colorless wax;  $[\alpha]_D^{20}$  –38.3 ( $c$  = 1.02, CH<sub>2</sub>Cl<sub>2</sub>);  $R_f$  0.33 (hexane/EtOAc, 1:3); IR  $\nu$  (neat) 3270, 2960, 2875, 1692, 1454, 1409, 1372, 1130, 1075, 1065, 947, 750, 703 cm<sup>-1</sup>; <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>)  $\delta$  7.32–7.23 (m, 2H), 7.22–7.12 (m, 3H), 4.24 (d,  $J$  = 9.2 Hz, 1H), 3.60–3.47 (m, 1H), 2.90 (dd,  $J$  = 17.7, 5.6 Hz, 1H), 2.84–2.70 (m, 1H), 2.75 (dd,  $J$  = 17.6, 4.4 Hz, 1H), 2.67–2.56 (m, 1H), 2.34 (td,  $J$  = 7.3, 4.2 Hz, 2H), 2.05–1.90 (m, 1H), 1.85–1.72 (m, 1H), 1.57 (q,  $J$  = 7.4 Hz, 2H), 1.23 (s, 9H), 0.89 (t,  $J$  = 7.4 Hz, 3H); <sup>13</sup>C{<sup>1</sup>H} NMR (100 MHz, CDCl<sub>3</sub>)  $\delta$  210.7 (C), 141.5 (C), 128.5 (CH), 128.4 (CH), 126.0 (CH), 56.0 (C), 53.4 (CH), 48.05 (CH<sub>2</sub>), 45.7 (CH<sub>2</sub>), 37.4 (CH<sub>2</sub>), 32.5 (CH<sub>2</sub>), 22.75 (CH<sub>3</sub>), 17.0 (CH<sub>2</sub>), 13.7 (CH<sub>3</sub>); LRMS (EI)  $m/z$  267 (M<sup>+</sup> – C<sub>4</sub>H<sub>8</sub>, 5%), 181 (9), 159 (30), 131 (13), 117 (25), 116 (15), 92 (9), 91 (100), 71 (15), 57 (26); HRMS (EI)  $m/z$  (M – C<sub>4</sub>H<sub>8</sub>)<sup>+</sup> calcd for C<sub>14</sub>H<sub>21</sub>NO<sub>2</sub>S 267.1293, found 267.1291.

## General Procedure for the Reaction of $\beta$ -Keto Amine Derivatives **5** with Aldehydes **2**.

**Synthesis of Compounds 7 and 8:** To a solution of the corresponding  $\beta$ -keto amine derivative **5** (0.2 mmol) in MeOH (2.0 mL) was added a 2M solution of HCl in Et<sub>2</sub>O (1.0 mL, 2.0 mmol) at 0 °C. The reaction mixture was stirred at the same temperature for 30 min. Complete formation of the corresponding free amine hydrochloride **6** was followed by TLC. After that, solvents were evaporated (15 Torr), and to the resulting residue was successively added L-proline (0.04 mmol), MgSO<sub>4</sub> (0.2 mmol), EtOH (2.0 mL), Et<sub>3</sub>N (0.2 mmol) and the corresponding aldehyde **2** (0.2 mmol). The resulting mixture was stirred for 6 h at rt (compounds **5a-h**) or at 60 °C (compounds **5i,j**). Then it was hydrolyzed with a saturated aqueous solution of NaHCO<sub>3</sub> (10 mL), and extracted with AcOEt (3  $\times$  15 mL). The organic phase was extracted with 0.15M HCl (3  $\times$  15 mL), and the resulting acidic aqueous phase was basified with a 1M NaOH aqueous solution (pH 9-10), and extracted with AcOEt (3  $\times$  15 mL). The new organic phase was dried with anhydrous MgSO<sub>4</sub>, and the solvent evaporated (15 Torr). The residue was purified by column chromatography (silica gel, hexane/EtOAc) to yield products **7** and **8**. Yields, physical and spectroscopic data follow.

**(2*R*,6*R*)-2-Phenethyl-6-phenylpiperidin-4-one (7a):** The representative procedure was followed by using  $\beta$ -keto amine derivative **5a** (59.0 mg, 0.2 mmol) and benzaldehyde (**2e**, 21.2 mg, 20.4  $\mu$ L, 0.2 mmol). Purification by column chromatography (CH<sub>2</sub>Cl<sub>2</sub>/MeOH, 99:1) yielded **7a** (43.0 mg,

0.154 mmol, 77%) as a yellow oil; 90:10 er [HPLC (Chiralpak AS-H column, hexane/*i*-PrOH = 90/10, 1.0 mL/min, 220 nm):  $t_{\text{minor}} = 14.13$  min,  $t_{\text{major}} = 16.22$  min];  $[\alpha]_{\text{D}}^{20} +40.1.8$  ( $c = 1.01$ , CH<sub>2</sub>Cl<sub>2</sub>);  $R_f$  0.30 (hexane/EtOAc, 5:1); IR  $\nu$  (neat) 3032, 2916, 1710, 1601, 1495, 1454, 1308, 1136, 1030, 750, 697 cm<sup>-1</sup>; <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>)  $\delta$  7.43–7.13 (m, 10H), 3.90 (dd,  $J = 7.4, 7.2$  Hz, 1H), 3.08–2.93 (m, 1H), 2.70 (t,  $J = 7.9$  Hz, 2H), 2.56–2.43 (m, 3H), 2.34–2.22 (m, 1H), 1.97–1.81 (m, 2H); <sup>13</sup>C{<sup>1</sup>H} NMR (75 MHz, CDCl<sub>3</sub>)  $\delta$  208.7 (C), 142.7 (C), 141.4 (C), 128.9 (CH), 128.6 (CH), 128.4 (CH), 128.0 (CH), 126.6 (CH), 126.2 (CH), 61.0 (CH<sub>2</sub>), 56.3 (CH), 50.4 (CH<sub>2</sub>), 48.2 (CH<sub>2</sub>), 38.6 (CH<sub>2</sub>), 32.1 (CH<sub>2</sub>); LRMS (EI)  $m/z$  279 (M<sup>+</sup>, 5%), 175 (30), 174 (62), 146 (14), 145 (11), 133 (10), 132(67), 131 (67), 117 (11), 116 (14), 105 (24), 104 (40), 103 (27), 91 (100), 78 (10), 77 (21), 65 (11), 51 (10); HRMS (EI)  $m/z$  M<sup>+</sup> calcd for C<sub>19</sub>H<sub>21</sub>NO 279.1623, found 279.1612.

**(2*S*,6*S*)-2-Phenethyl-6-phenylpiperidin-4-one (*ent*-7a):** The representative procedure was followed by using  $\beta$ -keto amine derivative **5e** (53.4 mg, 0.2 mmol) and 3-phenylpropanal (**2a**, 26.8 mg, 27.0  $\mu$ L, 0.2 mmol). Purification by column chromatography (CH<sub>2</sub>Cl<sub>2</sub>/MeOH, 99:1) yielded *ent*-7a (17.3 mg, 0.062 mmol, 31%), 88:12 er [HPLC (Chiralpak AS-H column, hexane/*i*-PrOH = 90/10, 1.0 mL/min, 220 nm):  $t_{\text{major}} = 15.33$  min,  $t_{\text{minor}} = 17.90$  min]. Physical and spectroscopical data were found to be the same as for **7a**.  $[\alpha]_{\text{D}}^{20} +34.6$  ( $c = 1.47$ , CH<sub>2</sub>Cl<sub>2</sub>).

**(2*S*,6*S*)-2-Phenethyl-6-phenylpiperidin-4-one (*ent*-7a):** The representative procedure was followed by using  $\beta$ -keto amine derivative *ent*-5a (59.0 mg, 0.2 mmol) and benzaldehyde (**2e**, 21.2 mg, 20.4  $\mu$ L, 0.2 mmol). Purification by column chromatography (CH<sub>2</sub>Cl<sub>2</sub>/MeOH, 99:1) yielded *ent*-7a (46.3 mg, 0.166 mmol, 83%), 91:9 er [HPLC (Chiralpak AS-H column, hexane/*i*-PrOH = 90/10, 1.0 mL/min, 220 nm):  $t_{\text{major}} = 15.65$  min,  $t_{\text{minor}} = 18.42$  min]. Physical and spectroscopical data were found to be the same as for **7a**.  $[\alpha]_{\text{D}}^{20} +35.4$  ( $c = 1.09$ , CH<sub>2</sub>Cl<sub>2</sub>).

**(2*R*,6*R*)-6-(2-Methylphenyl)-2-phenethylpiperidin-4-one (7b):** The representative procedure was followed by using  $\beta$ -keto amine derivative **5a** (59.0 mg, 0.2 mmol) and 2-methylbenzaldehyde (**2h**, 24.0 mg, 23.0  $\mu$ L, 0.2 mmol). Purification by column chromatography (CH<sub>2</sub>Cl<sub>2</sub>/MeOH, 99:1) yielded **7b** (40.4 mg, 0.138 mmol, 69%) as an orange oil; 94:6 er [HPLC (Chiralpak AS column, hexane/*i*-PrOH = 95/5, 1.0 mL/min, 220 nm):  $t_{\text{major}} = 15.05$  min,  $t_{\text{minor}} = 17.25$  min];  $[\alpha]_{\text{D}}^{20} +31.7$  ( $c = 1.08$ , CH<sub>2</sub>Cl<sub>2</sub>);  $R_f$  0.35 (hexane/EtOAc, 5:1); IR  $\nu$  (neat) 2925, 2858, 1710, 1601, 1494, 1454, 1287, 1044, 751, 699 cm<sup>-1</sup>; <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>)  $\delta$  7.57 (d,  $J = 7.4$  Hz, 1H), 7.34–7.11 (m, 8H), 4.12 (dd,  $J = 9.6, 5.1$  Hz, 1H), 3.09–2.94 (m, 1H), 2.71 (dd,  $J = 9.3, 6.7$  Hz, 2H), 2.53–2.38 (m, 4H), 2.34 (s, 3H), 2.30–2.22 (m, 1H), 1.94–1.84 (m, 2H); <sup>13</sup>C{<sup>1</sup>H} NMR (75 MHz, CDCl<sub>3</sub>)  $\delta$  209.0 (C), 141.4 (C), 140.7 (C), 135.1 (C), 130.7 (CH), 128.6 (CH), 128.4 (CH), 127.5 (CH), 126.7 (CH), 126.2 (CH), 125.6 (CH), 56.7 (CH), 56.45 (CH), 49.2 (CH<sub>2</sub>), 48.3 (CH<sub>2</sub>), 38.6 (CH<sub>2</sub>), 32.1 (CH<sub>2</sub>), 19.2 (CH<sub>3</sub>); LRMS (EI)  $m/z$  293 (M<sup>+</sup>, 3%), 188 (13), 146 (25), 145 (50), 131 (9), 118 (14),

117 (24), 116 (24), 115 (21), 92 (10), 91 (100), 65 (12); HRMS (EI)  $m/z$   $M^+$  calcd for  $C_{20}H_{23}NO$  293.1780, found 293.1778.

**(2*R*,6*R*)-2-(4-Methoxyphenyl)-6-phenethylpiperidin-4-one (7c):** The representative procedure was followed by using  $\beta$ -keto amine derivative **5a** (59.0 mg, 0.2 mmol) and 4-methoxybenzaldehyde (**2i**, 27.2 mg, 22.8  $\mu$ L, 0.2 mmol). Purification by column chromatography ( $CH_2Cl_2/MeOH$ , 99:1) yielded **7c** (39.5 mg, 0.128 mmol, 64%) as an orange oil; 88:12 er [HPLC (Chiralpak AD-H column, hexane/*i*-PrOH = 90/10, 1.0 mL/min, 220 nm):  $t_{minor}$  = 10.01 min,  $t_{major}$  = 11.93 min];  $[\alpha]_D^{20}$  +23.1 ( $c$  = 1.01,  $CH_2Cl_2$ );  $R_f$  0.16 (hexane/EtOAc, 5:1); IR  $\nu$  (neat) 2918, 2849, 1711, 1610, 1512, 1454, 1246, 1176, 1032, 831, 748, 699  $cm^{-1}$ ;  $^1H$  NMR (300 MHz,  $CDCl_3$ )  $\delta$  7.35–7.12 (m, 7H), 6.89 (d,  $J$  = 8.7 Hz, 2H), 3.89–3.82 (m, 1H), 3.80 (s, 3H), 3.06–2.91 (m, 1H), 2.70 (t,  $J$  = 8.0 Hz, 2H), 2.53–2.41 (m, 2H), 2.33–2.18 (m, 2H), 1.95–1.80 (m, 2H);  $^{13}C\{^1H\}$  NMR (75 MHz,  $CDCl_3$ )  $\delta$  208.9 (C), 159.3 (C), 141.4 (C), 134.9 (C), 128.6 (CH), 128.4 (CH), 127.75 (CH), 126.2 (CH), 114.2 (CH), 60.4 (CH), 56.3 (CH<sub>3</sub>), 55.4 (CH), 50.45 (CH<sub>2</sub>), 48.1 (CH<sub>2</sub>), 38.6 (CH<sub>2</sub>), 32.1 (CH<sub>2</sub>); LRMS (EI)  $m/z$  309 ( $M^+$ , 2%), 205 (9), 162 (28), 161 (41), 135 (12), 134 (22), 133 (13), 131 (9), 116 (17), 92 (10), 91 (100), 65 (11); HRMS (EI)  $m/z$   $M^+$  calcd for  $C_{20}H_{23}NO_2$  309.1729, found 309.1711.

**(2*S*,6*R*)-2-Nonyl-6-phenethylpiperidin-4-one (7d):** The representative procedure was followed by using  $\beta$ -keto amine derivative **5a** (59.0 mg, 0.2 mmol) and decanal (**2d**, 31.0 mg, 37.6  $\mu$ L, 0.2 mmol). Purification by column chromatography ( $CH_2Cl_2/MeOH$ , 99:1) yielded **7d** (27.0 mg, 0.082 mmol, 41%) as a yellow solid; mp 41–42 °C (hexane/ $CH_2Cl_2$ ); 89:11 er [HPLC (Chiralcel OJ column, hexane/*i*-PrOH = 95/5, 1.0 mL/min, 210 nm):  $t_{minor}$  = 10.38 min,  $t_{major}$  = 25.50 min];  $[\alpha]_D^{20}$  –1.7 ( $c$  = 1.04,  $CH_2Cl_2$ );  $R_f$  0.23 (hexane/EtOAc, 5:1); IR  $\nu$  (neat) 2922, 2852, 1709, 1602, 1495, 1455, 1324, 1071, 747, 697  $cm^{-1}$ ;  $^1H$  NMR (300 MHz,  $CDCl_3$ )  $\delta$  7.35–7.13 (m, 5H), 2.91–2.74 (m, 2H), 2.70 (t,  $J$  = 7.0 Hz, 2H), 2.49–2.32 (m, 2H), 2.24–2.01 (m, 2H), 1.98–1.75 (m, 2H), 1.61–1.39 (m, 2H), 1.27 (s, 14H), 0.88 (t,  $J$  = 6.8 Hz, 3H);  $^{13}C\{^1H\}$  NMR (100 MHz,  $CDCl_3$ )  $\delta$  209.4 (C), 141.4 (C), 128.6 (CH), 128.35 (CH), 126.15 (CH), 56.6 (CH), 56.1 (CH), 48.7 (CH<sub>2</sub>), 48.6 (CH<sub>2</sub>), 38.5 (CH<sub>2</sub>), 37.05 (CH<sub>2</sub>), 32.3 (CH<sub>2</sub>), 31.9 (CH<sub>2</sub>), 29.7 (CH<sub>2</sub>), 29.6 (CH<sub>2</sub>), 29.4 (CH<sub>2</sub>), 25.75 (CH<sub>2</sub>), 22.7 (CH<sub>2</sub>), 14.2 (CH<sub>3</sub>); LRMS (EI)  $m/z$  329 ( $M^+$ , 2%), 225 (8), 224 (50), 203 (10), 202 (73) 182 (24), 160 (21), 116 (16), 97 (11), 92 (8), 91 (100), 71 (8), 55 (15); HRMS (EI)  $m/z$   $M^+$  calcd for  $C_{22}H_{35}NO$  329.2719, found 329.2697.

**(2*R*,6*S*)-2-Nonyl-6-phenethylpiperidin-4-one (ent-7d):** The representative procedure was followed by using  $\beta$ -keto amine derivative **5d** (63.4 mg, 0.2 mmol) and 3-phenylpropanal (**2a**, 26.8 mg, 27.0  $\mu$ L, 0.2 mmol). Purification by column chromatography ( $CH_2Cl_2/MeOH$ , 99:1) yielded **ent-7d** (40.8 mg, 0.124 mmol, 62%), 93:7 er [HPLC (Chiralcel OJ column, hexane/*i*-PrOH = 95/5,



1.0 mL/min, 210 nm):  $t_{\text{major}} = 11.22$  min,  $t_{\text{minor}} = 25.92$  min]. Physical and spectroscopical data were found to be the same as for **7d**.  $[\alpha]_{\text{D}}^{20} +0.9$  ( $c = 1.05$ ,  $\text{CH}_2\text{Cl}_2$ ).

**(2S,6R)-2-Butyl-6-phenethylpiperidin-4-one (7e)**: The representative procedure was followed by using  $\beta$ -keto amine derivative **5a** (56.1 mg, 0.19 mmol) and pentanal (**2j**, 17.2 mg, 21.5  $\mu\text{L}$ , 0.2 mmol). Purification by column chromatography ( $\text{CH}_2\text{Cl}_2/\text{MeOH}$ , 99:1) yielded **7e** (27.6 mg, 0.106 mmol, 56%) as an orange oil; 93:7 er [HPLC (Chiralpak AS-H column, hexane/*i*-PrOH = 90/10, 1.0 mL/min, 210 nm):  $t_{\text{minor}} = 7.94$  min,  $t_{\text{major}} = 9.46$  min];  $[\alpha]_{\text{D}}^{20} -0.7$  ( $c = 1.03$ ,  $\text{CH}_2\text{Cl}_2$ );  $R_f$  0.16 (hexane/EtOAc, 5:1); IR  $\nu$  (neat) 2927, 2859, 1711, 1603, 1496, 1454, 1275, 1030, 748, 699  $\text{cm}^{-1}$ ;  $^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ )  $\delta$  7.35–7.12 (m, 5H), 2.89–2.62 (m, 2H), 2.71 (t,  $J = 7.8$  Hz, 1H), 2.44–2.32 (m, 1H), 2.28–1.98 (m, 2H), 1.93–1.71 (m, 2H), 1.58–1.40 (m, 2H), 1.40–1.15 (m, 6H), 0.91 (t,  $J = 6.9$  Hz, 3H);  $^{13}\text{C}\{^1\text{H}\}$  NMR (75 MHz,  $\text{CDCl}_3$ )  $\delta$  209.5 (C), 141.4 (C), 128.65 (CH), 128.4 (CH), 126.2 (CH), 56.6 (CH), 56.2 (CH), 48.7 ( $\text{CH}_2$ ), 48.7 ( $\text{CH}_2$ ), 38.5 ( $\text{CH}_2$ ), 36.8 ( $\text{CH}_2$ ), 32.3 ( $\text{CH}_2$ ), 28.0 ( $\text{CH}_2$ ), 22.8 ( $\text{CH}_2$ ), 14.1 ( $\text{CH}_3$ ); LRMS (EI)  $m/z$  259 ( $\text{M}^+$ , 2%) 203 (9), 202 (68), 160 (33), 154 (55), 117 (11), 116 (13), 112 (36), 111 (9), 92 (8), 91 (100), 65 (9), 55 (15); HRMS (EI)  $m/z$   $\text{M}^+$  calcd for  $\text{C}_{17}\text{H}_{25}\text{NO}$  259.1936, found 259.1915.

**(2R,6S)-2-Methyl-6-nonylpiperidin-4-one (7f)**: The representative procedure was followed by using  $\beta$ -keto amine derivative **5b** (61.5 mg, 0.3 mmol) and decanal (**2d**, 46.8 mg, 56.4  $\mu\text{L}$ , 0.3 mmol). Purification by column chromatography ( $\text{CH}_2\text{Cl}_2/\text{MeOH}$ , 99:1) yielded **7f** (42.3 mg, 0.177 mmol, 59%) as a yellow wax; 90:10 er [GC (CP-Chirasil-Dex CB column,  $T_{\text{injector}} = 275$   $^{\circ}\text{C}$ ,  $T_{\text{detector}} = 250$   $^{\circ}\text{C}$ ,  $T_{\text{column}} = 100$   $^{\circ}\text{C}$  (10 min) and 100–200  $^{\circ}\text{C}$  (2.5  $^{\circ}\text{C}/\text{min}$ ),  $P = 101$  kPa):  $t_{\text{major}} = 42.49$  min,  $t_{\text{minor}} = 42.70$  min];  $[\alpha]_{\text{D}}^{20} -2.9$  ( $c = 1.42$ ,  $\text{CH}_2\text{Cl}_2$ );  $R_f$  0.24 (EtOAc); IR  $\nu$  (neat) 2924, 2853, 1718, 1542, 1460, 1377, 1280, 1142, 1077, 722  $\text{cm}^{-1}$ ;  $^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ )  $\delta$  3.06–2.88 (m, 1H), 2.92–2.76 (m, 1H), 2.41–2.30 (m, 2H), 2.14–1.99 (m, 2H), 1.59–1.23 (m, 16H), 1.22 (d,  $J = 6.2$  Hz, 3H), 0.88 (t,  $J = 6.8$  Hz, 3H);  $^{13}\text{C}\{^1\text{H}\}$  NMR (100 MHz,  $\text{CDCl}_3$ )  $\delta$  209.6 (C), 52.3 (CH), 50.2 (CH), 48.1 ( $\text{CH}_2$ ), 37.1 ( $\text{CH}_2$ ), 32.0 ( $\text{CH}_2$ ), 29.7 ( $\text{CH}_2$ ), 29.6 ( $\text{CH}_2$ ), 29.4 ( $\text{CH}_2$ ), 25.8 ( $\text{CH}_2$ ), 22.8 ( $\text{CH}_2$ ), 22.7 ( $\text{CH}_3$ ), 14.2 ( $\text{CH}_3$ ); LRMS (EI)  $m/z$  224 ( $\text{M}^+ - \text{CH}_3$ , 2%), 182 (7), 113 (7), 112 (100), 70 (30); HRMS (EI)  $m/z$   $\text{M}^+$  calcd for  $\text{C}_{15}\text{H}_{29}\text{NO}$  239.2249, found 239.2247.

**(2R,6R)-2-Isopropyl-6-methylpiperidin-4-one (7g)**: The representative procedure was followed by using  $\beta$ -keto amine derivative **5b** (61.5 mg, 0.3 mmol) and isobutyraldehyde (**2c**, 25.5 mg, 31.9  $\mu\text{L}$ , 0.35 mmol). Purification by column chromatography ( $\text{CH}_2\text{Cl}_2/\text{MeOH}$ , 99:1) yielded **7g** (33.5 mg, 0.216 mmol, 72%) as a yellow oil; 92:8 er [GC (CP-Chirasil-Dex CB column,  $T_{\text{injector}} = 275$   $^{\circ}\text{C}$ ,  $T_{\text{detector}} = 250$   $^{\circ}\text{C}$ ,  $T_{\text{column}} = 100$   $^{\circ}\text{C}$  (10 min) and 100–200  $^{\circ}\text{C}$  (2.5  $^{\circ}\text{C}/\text{min}$ ),  $P = 101$  kPa):  $t_{\text{minor}} = 15.36$  min,  $t_{\text{major}} = 15.79$  min];  $[\alpha]_{\text{D}}^{20} -3.0$  ( $c = 0.62$ ,  $\text{CH}_2\text{Cl}_2$ );  $R_f$  0.28 (hexane/EtOAc, 1:1); IR  $\nu$  (neat) 2961, 2928, 2874, 1718, 1464, 1377, 1308, 1287, 1117, 751  $\text{cm}^{-1}$ ;  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$

2.95 (dq,  $J = 12.2, 6.2, 2.9$  Hz, 1H), 2.63 (ddd,  $J = 11.9, 6.0, 2.8$  Hz, 1H), 2.41–2.29 (m, 2H), 2.14–2.03 (m, 2H), 1.80–1.64 (m,  $J = 6.5$  Hz, 1H), 1.22 (d,  $J = 6.2$  Hz, 3H), 0.97 (d,  $J = 6.8$  Hz, 3H), 0.94 (d,  $J = 6.8$  Hz, 3H);  $^{13}\text{C}\{^1\text{H}\}$  NMR (100 MHz,  $\text{CDCl}_3$ )  $\delta$  210.3 (C), 62.3 (CH), 52.3 (CH), 50.2 ( $\text{CH}_2$ ), 45.0 ( $\text{CH}_2$ ), 33.2 (CH), 22.7 ( $\text{CH}_3$ ), 19.1 ( $\text{CH}_3$ ), 18.4 ( $\text{CH}_3$ ); LRMS (EI)  $m/z$  154 ( $\text{M}^+ - \text{H}$ , 1%), 112 (100), 98 (13), 70 (97); HRMS (EI)  $m/z$  ( $\text{M} - \text{H}$ ) $^+$  calcd for  $\text{C}_9\text{H}_{16}\text{NO}$  154.1232, found 154.1227.

**(2*S*,6*R*)-2-Isopropyl-6-phenylpiperidin-4-one (7h)**: The representative procedure was followed by using  $\beta$ -keto amine derivative **5c** (65.2 mg, 0.28 mmol) and benzaldehyde (**2e**, 29.7 mg, 30.0  $\mu\text{L}$ , 0.28 mmol). Purification by column chromatography ( $\text{CH}_2\text{Cl}_2/\text{MeOH}$ , 99:1) yielded **7h** (46.2 mg, 0.213 mmol, 76%) as an orange oil; 72:28 er [HPLC (Chiralpak AS column, hexane/*i*-PrOH = 95/5, 1.0 mL/min, 210 nm):  $t_{\text{minor}} = 13.49$  min,  $t_{\text{major}} = 17.20$  min];  $[\alpha]_{\text{D}}^{20} +27.8$  ( $c = 1.02$ ,  $\text{CH}_2\text{Cl}_2$ );  $R_f$  0.46 (hexane/EtOAc, 5:1); IR  $\nu$  (neat) 2961, 2876, 1714, 1456, 1365, 1249, 1030, 756, 699  $\text{cm}^{-1}$ ;  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  7.45–7.24 (m, 5H), 3.90 (dd,  $J = 9.7, 5.2$  Hz, 1H), 2.77 (ddd,  $J = 11.7, 5.7, 2.9$  Hz, 1H), 2.52–2.44 (m, 2H), 2.46–2.37 (m, 1H), 2.30–2.19 (m, 1H), 1.83–1.69 (m, 1H), 0.99 (d,  $J = 6.8$  Hz, 3H), 0.98 (d,  $J = 6.8$  Hz, 3H);  $^{13}\text{C}\{^1\text{H}\}$  NMR (100 MHz,  $\text{CDCl}_3$ )  $\delta$  209.7 (C), 143.1 (C), 128.8 (CH), 127.9 (CH), 126.6 (CH), 62.4 (CH), 61.1 (CH), 50.6 ( $\text{CH}_2$ ), 45.0 ( $\text{CH}_2$ ), 33.2 (CH), 18.8 ( $\text{CH}_3$ ), 18.3 ( $\text{CH}_3$ ); LRMS (EI)  $m/z$  217 ( $\text{M}^+$ , 2%) 175 (12), 174 (100), 132 (53), 131 (88), 105 (17), 104 (28), 103 (26), 77 (12), 70 (13); HRMS (EI)  $m/z$   $\text{M}^+$  calcd for  $\text{C}_{14}\text{H}_{19}\text{NO}$  217.1467, found 217.1465.

**(2*R*,6*S*)-2-Isopropyl-6-phenylpiperidin-4-one (ent-7h)**: The representative procedure was followed by using  $\beta$ -keto amine derivative **5e** (47.6 mg, 0.178 mmol) and isobutyraldehyde (**2c**, 13.0 mg, 16.4  $\mu\text{L}$ , 0.18 mmol). Purification by column chromatography ( $\text{CH}_2\text{Cl}_2/\text{MeOH}$ , 99:1) yielded *ent*-**7h** (28.2 mg, 0.130 mmol, 73%), 78:22 er [HPLC (Chiralpak AS column, hexane/*i*-PrOH = 95/5, 1.0 mL/min, 210 nm):  $t_{\text{major}} = 13.16$  min,  $t_{\text{minor}} = 17.05$  min]. Physical and spectroscopical data were found to be the same as for **7h**.  $[\alpha]_{\text{D}}^{20} -42.8$  ( $c = 0.93$ ,  $\text{CH}_2\text{Cl}_2$ ).

**(2*R*,6*S*)-2-(4-Bromophenyl)-6-phenylpiperidin-4-one (7i)**: The representative procedure was followed by using  $\beta$ -keto amine derivative **5e** (53.4 mg, 0.2 mmol) and 4-bromobenzaldehyde (**2f**, 37.0 mg, 0.2 mmol). Purification by column chromatography ( $\text{CH}_2\text{Cl}_2/\text{MeOH}$ , 99:1) yielded **7i** (50.2 mg, 0.152 mmol, 76%) as an orange wax; 56:44 er [HPLC (Chiralpak IA column, hexane/*i*-PrOH = 90/10, 1.0 mL/min, 220 nm):  $t_{\text{major}} = 14.57$  min,  $t_{\text{minor}} = 17.60$  min];  $[\alpha]_{\text{D}}^{20} +1.4$  ( $c = 1.03$ ,  $\text{CH}_2\text{Cl}_2$ );  $R_f$  0.49 (hexane/EtOAc, 5:1); IR  $\nu$  (neat) 2964, 2834, 1709, 1487, 1455, 1296, 1239, 1071, 1010, 828, 757, 699  $\text{cm}^{-1}$ ;  $^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ )  $\delta$  7.53–7.25 (m, 9H), 4.10–4.00 (m, 2H), 2.63–2.48 (m, 4H);  $^{13}\text{C}\{^1\text{H}\}$  NMR (75 MHz,  $\text{CDCl}_3$ )  $\delta$  207.6 (C), 142.6 (C), 141.8 (C), 132.0 (CH), 128.9 (CH), 128.4 (CH), 128.1 (CH), 126.7 (CH), 121.75 (CH), 61.2 (CH), 60.6 (CH), 50.4 ( $\text{CH}_2$ );

LRMS (EI)  $m/z$  331 ( $M^+$ , 15%), 329 (14), 211 (53), 209 (52), 184 (69), 183 (36), 182 (50), 181 (23), 146 (49), 145 (90), 132 (21), 131 (67), 106 (35), 105 (36), 104 (100), 103 (93), 102 (80), 78 (20), 77 (60), 76 (27), 75 (25); HRMS (EI)  $m/z$   $M^+$  calcd for  $C_{17}H_{16}BrNO$  329.0415, found 329.0394.

**(2*S*,6*R*)-2-(4-Bromophenyl)-6-phenylpiperidin-4-one (ent-7i)**: The representative procedure was followed by using  $\beta$ -keto amine derivative **5f** (44.8 mg, 0.13 mmol) and benzaldehyde (**2e**, 13.8 mg, 13.8  $\mu$ L, 0.13 mmol). Purification by column chromatography ( $CH_2Cl_2/MeOH$ , 99:1) yielded **ent-7i** (31.2 mg, 0.095 mmol, 73%), 53:47 er [HPLC (Chiralpak IA column, hexane/*i*-PrOH = 90/10, 1.0 mL/min, 220 nm):  $t_{minor}$  = 14.56 min,  $t_{major}$  = 17.70 min]. Physical and spectroscopical data were found to be the same as for **7i**.  $[\alpha]_D^{20}$  -5.1 ( $c$  = 1.03,  $CH_2Cl_2$ ).

**(4*R*,9*aR*)-4-(3,4-Dimethoxyphenyl)octahydro-2*H*-quinolizin-2-one (7j)**: The representative procedure was followed by using  $\beta$ -keto amine derivative **5g** (65.0 mg, 0.2 mmol) and 3,4-dimethoxybenzaldehyde (**2k**, 33.2 mg, 0.2 mmol). Purification by column chromatography ( $CH_2Cl_2/MeOH$ , 99:1) yielded **7j** (17.9 mg, 0.062 mmol, 31%) as a yellow oil; 93:7 er [HPLC (Chiralcel OJ column, hexane/*i*-PrOH = 90/10, 1.0 mL/min, 220 nm):  $t_{minor}$  = 10.58 min,  $t_{major}$  = 16.10 min];  $[\alpha]_D^{20}$  +54.3 ( $c$  = 0.87,  $CH_2Cl_2$ );  $R_f$  0.18 (hexane/EtOAc, 1:1); IR  $\nu$  (neat) 2933, 1719, 1594, 1511, 1463, 1264, 1138, 1027  $cm^{-1}$ ;  $^1H$  NMR (400 MHz,  $CDCl_3$ )  $\delta$  6.92 (s, 1H), 6.88–6.78 (m, 2H), 3.90 (s, 3H), 3.87 (s, 3H), 3.21 (dd,  $J$  = 12.2, 3.2 Hz, 1H), 2.79 (d,  $J$  = 11.5 Hz, 1H), 2.70 (t,  $J$  = 13.7 Hz, 1H), 2.52 (t,  $J$  = 13.2 Hz, 1H), 2.46–2.23 (m, 3H), 1.78–1.64 (m, 2H), 1.66–1.60 (m, 1H), 1.60–1.41 (m, 3H), 1.38–1.24 (m, 1H);  $^{13}C\{^1H\}$  NMR (100 MHz,  $CDCl_3$ )  $\delta$  208.0 (C), 149.45 (C), 148.5 (C), 135.15 (C), 119.7 (CH), 111.1 (CH), 109.9 (CH), 70.1 (CH), 62.6 (CH), 56.1 (CH<sub>3</sub>), 56.0 (CH<sub>3</sub>), 52.9 (CH<sub>2</sub>), 50.9 (CH<sub>2</sub>), 48.8 (CH<sub>2</sub>), 34.4 (CH<sub>2</sub>), 25.9 (CH<sub>2</sub>), 24.3 (CH<sub>2</sub>); LRMS (EI)  $m/z$  289 ( $M^+$ , 22%) 247 (16), 209 (16), 208 (39), 207 (62), 206 (43), 192 (62), 191 (100), 177 (16), 176 (27), 175 (17), 165 (47), 164 (85), 163 (18), 84 (49), 83 (27), 82 (24), 55 (44); HRMS (EI)  $m/z$   $M^+$  calcd for  $C_{17}H_{23}NO_3$  289.1678, found 289.1671.

**(4*S*,9*aS*)-4-(3,4-Dimethoxyphenyl)octahydro-2*H*-quinolizin-2-one (ent-7j)**: The representative procedure was followed by using  $\beta$ -keto amine derivative **ent-5h** (56.2 mg, 0.2 mmol) and 3,4-dimethoxybenzaldehyde (**2k**, 33.2 mg, 0.2 mmol). Purification by column chromatography ( $CH_2Cl_2/MeOH$ , 99:1) yielded **ent-7j** (37.6 mg, 0.130 mmol, 65%), 93:7 er [HPLC (Chiralcel OJ column, hexane/*i*-PrOH = 90/10, 1.0 mL/min, 220 nm):  $t_{major}$  = 10.45 min,  $t_{minor}$  = 16.32 min]. Physical and spectroscopical data were found to be the same as for **7j**.  $[\alpha]_D^{20}$  -56.9 ( $c$  = 0.89,  $CH_2Cl_2$ ).

**(-)-Epimyrtnine Hydrochloride (7k·HCl)**: The representative procedure was followed by using  $\beta$ -keto amine derivative **5b** (41.0 mg, 0.2 mmol) and 5-chloropentanal (**2l**, 30.1 mg, 0.25 mmol). Final extraction in this case was carried out with  $CH_2Cl_2$  (3  $\times$  10 mL). The organic phase containing (-)-

epimyrte [GC-MS: single peak,  $m/z$  167 ( $M^+$ , 26%)] was treated with a 2M HCl solution in Et<sub>2</sub>O (0.5 mL, 1.0 mmol) for 15 min, and after that the solvents were evaporated (15 Torr) to yield (–)-epimyrte hydrochloride as a white solid (26.8 mg, 0.132 mmol, 66%); 93:7 er (**7k**) [GC (CP-Chirasil-Dex CB column,  $T_{\text{injector}} = 275$  °C,  $T_{\text{detector}} = 250$  °C,  $T_{\text{column}} = 100$  °C (10 min) and 100–200 °C (2.5 °C/min),  $P = 101$  kPa):  $t_{\text{minor}} = 25.23$  min,  $t_{\text{major}} = 25.81$  min];  $[\alpha]_{\text{D}}^{20} -13.4$  ( $c = 0.40$ , CHCl<sub>3</sub>) [lit.<sup>11a</sup>  $[\alpha]_{\text{D}}^{20} -17.4$  ( $c = 0.7$ , CHCl<sub>3</sub>)]; <sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>)  $\delta$  12.92 (s, 1H), 3.94 (d,  $J = 11.3$  Hz, 1H), 3.58 – 3.44 (m, 1H), 3.45 – 3.25 (m, 2H), 3.22 – 3.00 (m, 1H), 2.61 – 2.47 (m, 3H), 2.43 – 2.21 (m, 2H), 2.03 – 1.84 (m, 2H), 1.65 (d,  $J = 5.7$  Hz, 3H), 1.60 – 1.43 (m, 2H); <sup>13</sup>C{<sup>1</sup>H} NMR (75 MHz, CDCl<sub>3</sub>)  $\delta$  201.45(C), 63.74 (CH), 61.50 (CH), 51.45 (CH<sub>2</sub>), 46.49 (CH<sub>2</sub>), 45.46 (CH<sub>2</sub>), 30.84 (CH<sub>2</sub>), 23.09(CH<sub>2</sub>), 22.37 (CH<sub>2</sub>), 17.70 (CH<sub>3</sub>); LRMS (EI)  $m/z$  167 (**7k**,  $M^+$ , 26%) 153 (10), 152 (100), 124 (34), 110 (71), 84 (9), 83 (31), 82 (14), 69 (15), 55 (16).

**(2R,3S,6R)-3-methyl-6-phenethyl-2-phenylpiperidin-4-one (8a)**: The representative procedure was followed by using  $\beta$ -keto amine derivative **5i** (52.5 mg, 0.17 mmol) and benzaldehyde (**2e**, 21.2 mg, 20.4  $\mu$ L, 0.2 mmol). Purification by column chromatography (CH<sub>2</sub>Cl<sub>2</sub>/MeOH, 99:1) yielded **8a** (33.9 mg, 0.116 mmol, 68%) as a white solid; mp 71–72 °C (hexane/CH<sub>2</sub>Cl<sub>2</sub>); 94:6 er [HPLC (Chiralpak AS-H column, hexane/*i*-PrOH = 95/5, 1.0 mL/min, 220 nm):  $t_{\text{minor}} = 9.28$  min,  $t_{\text{major}} = 11.60$  min];  $[\alpha]_{\text{D}}^{20} +21.5$  ( $c = 1.02$ , CH<sub>2</sub>Cl<sub>2</sub>);  $R_f$  0.42 (hexane/EtOAc, 5:1); IR  $\nu$  (neat) 2928, 1703, 1602, 1494, 1451, 1332, 1238, 934, 835, 748, 696 cm<sup>–1</sup>; <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>)  $\delta$  7.43–7.12 (m, 10H), 3.46 (d,  $J = 10.5$  Hz, 1H), 3.07–2.95 (m, 1H), 2.67 (t,  $J = 8.0$  Hz, 2H), 2.59 (dq,  $J = 10.7$ , 6.5 Hz, 1H), 2.54 (dd,  $J = 13.2$ , 2.9 Hz, 1H), 2.39 (t,  $J = 12.4$  Hz, 1H), 1.91–1.80 (m, 2H), 0.77 (d,  $J = 6.6$  Hz, 3H); <sup>13</sup>C{<sup>1</sup>H} NMR (100 MHz, CDCl<sub>3</sub>)  $\delta$  210.1 (C), 141.9 (C), 141.4 (C), 128.8 (CH), 128.6 (CH), 128.4 (CH), 128.1 (CH), 127.8 (CH), 126.2 (CH), 68.4 (CH), 56.8 (CH), 51.7 (CH), 48.6 (CH<sub>2</sub>), 38.6 (CH<sub>2</sub>), 32.0 (CH<sub>2</sub>), 10.3 (CH<sub>3</sub>); LRMS (EI)  $m/z$  293 ( $M^+$ , 10%), 188 (16), 160 (11), 159 (30), 132 (38), 117 (23), 116 (18), 115 (18), 105 (14), 104 (16), 91 (100), 65 (10); HRMS (ESI)  $m/z$   $M^+$  calcd for C<sub>20</sub>H<sub>23</sub>NO 293.1780, found 293.1779.

**(2R,3S,6R)-3-Ethyl-6-phenethyl-2-phenylpiperidin-4-one (8b)**: The representative procedure was followed by using  $\beta$ -keto amine derivative **5j** (64.6 mg, 0.2 mmol) and benzaldehyde (**2e**, 48 mg, 0.2 mmol). Purification by column chromatography (CH<sub>2</sub>Cl<sub>2</sub>/MeOH, 99:1) yielded **8b** (22.7 mg, 0.074 mmol, 37%) as a yellow oil; 91:9 er [HPLC (Chiralpak AS-H column, hexane/*i*-PrOH = 95/5, 1.0 mL/min, 220 nm):  $t_{\text{minor}} = 7.08$  min,  $t_{\text{major}} = 8.68$  min];  $[\alpha]_{\text{D}}^{20} +16.7$  ( $c = 0.89$ , CH<sub>2</sub>Cl<sub>2</sub>);  $R_f$  0.49 (hexane/EtOAc, 5:1); IR  $\nu$  (neat) 2927, 1708, 1495, 1455, 1307, 1207, 1029, 748, 698 cm<sup>–1</sup>; <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>)  $\delta$  7.45–7.24 (m, 7H), 7.26–7.13 (m, 3H), 3.60 (d,  $J = 10.7$  Hz, 1H), 3.10–2.95 (m, 1H), 2.75–2.63 (m, 2H), 2.60–2.47 (m, 1H), 2.47–2.34 (m, 1H), 1.97–1.80 (m, 3H), 1.62–1.41 (m, 1H), 1.22–1.03 (m, 1H), 0.76 (t,  $J = 7.4$  Hz, 3H); <sup>13</sup>C{<sup>1</sup>H} NMR (100 MHz, CDCl<sub>3</sub>)  $\delta$

209.8 (C), 141.9 (C), 141.5 (C), 128.8 (CH), 128.6 (CH), 128.4 (CH), 128.1 (CH), 127.9 (CH), 126.15 (CH), 66.7 (CH), 58.5 (CH), 57.0 (CH), 49.3 (CH<sub>2</sub>), 38.6 (CH<sub>2</sub>), 32.05 (CH<sub>2</sub>), 18.1 (CH<sub>2</sub>), 12.3 (CH<sub>3</sub>); LRMS (EI)  $m/z$  307 (M<sup>+</sup>, 9%), 292 (15), 202 (10), 159 (31), 132 (27), 131 (14), 117 (11), 116 (16), 106 (9), 105 (15), 104 (17), 91 (100); HRMS (ESI)  $m/z$  M<sup>+</sup> calcd for C<sub>21</sub>H<sub>25</sub>NO 307.1936, found 307.1932.

**Synthesis of Alkaloid (+)-241D (11) from Piperidin-4-one 7f:** To solution of piperidin-4-one **7f** (71.7 mg, 0.3 mmol) in MeOH (5 mL) was added a 2M LiBH<sub>4</sub> solution in MeOH (0.5 mL, 1.0 mmol) at 0 °C. The reaction mixture was stirred for 1 h at the same temperature. Then it was hydrolyzed with a 2M NaOH aqueous solution (10 mL), and extracted with CH<sub>2</sub>Cl<sub>2</sub> (4 × 15 mL). The organic phase was dried with anhydrous MgSO<sub>4</sub>, and the solvent evaporated (15 Torr). The residue was purified by recrystallization with petroleum ether to give (–)-241D (**11**) (48.2 mg, 0.20 mmol, 69%) as a white solid; mp 103–106 °C (hexane/CH<sub>2</sub>Cl<sub>2</sub>) (lit.<sup>15b</sup> mp 106 °C); >95:5 er [GC (CP-Chirasil-Dex CB column, T<sub>injector</sub> = 275 °C, T<sub>detector</sub> = 250 °C, T<sub>column</sub> = 100 °C (10 min) and 100–200 °C (2.5 °C/min), P = 101 kPa): t<sub>major</sub> = 45.14 min]; [α]<sub>D</sub><sup>20</sup> +5.2 (*c* = 0.52, MeOH) [lit.<sup>15c</sup> [α]<sub>D</sub><sup>20</sup> +5.4 (*c* = 0.5, MeOH)]; R<sub>f</sub> 0.35 (CH<sub>2</sub>Cl<sub>2</sub>/MeOH, 10:1); IR ν (neat) 3268, 3175, 2919, 2850, 1469, 1379, 1320, 1156, 1111, 1035, 838 cm<sup>–1</sup>; <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>) δ 3.74–3.58 (m, 1H), 2.77–2.60 (m, 1H), 2.62–2.47 (m, 1H), 2.05–1.88 (m, 2H), 1.56–1.47 (m, 2H), 1.44–1.36 (m, 2H), 1.34–1.20 (m, 14H), 1.12 (d, *J* = 6.3 Hz, 3H), 1.08–0.92 (m, 2H), 0.88 (t, *J* = 6.8 Hz, 3H); <sup>13</sup>C{<sup>1</sup>H} NMR (100 MHz, CDCl<sub>3</sub>) δ 69.55 (CH), 55.0 (CH), 50.3 (CH), 44.05 (CH<sub>2</sub>), 41.9 (CH<sub>2</sub>), 36.95 (CH<sub>2</sub>), 32.0 (CH<sub>2</sub>), 29.9 (CH<sub>2</sub>), 29.7 (CH<sub>2</sub>), 29.7 (CH<sub>2</sub>), 29.45 (CH<sub>2</sub>), 26.2 (CH<sub>2</sub>), 22.8 (CH<sub>2</sub>), 22.6 (CH<sub>3</sub>), 14.3 (CH<sub>3</sub>); LRMS (EI)  $m/z$  226 (M<sup>+</sup>–CH<sub>3</sub>, 3%) 182 (29), 115 (8), 114 (100), 107 (11), 70 (27), 69 (7), 55 (6).

**Synthesis of (–)-Lasubine II (12) from Piperidin-4-one ent-7j:** To solution of piperidin-4-one *ent*-**7j** (28.9 mg, 0.1 mmol) in dry THF (2 mL) was added dropwise a 2M L-Selectride solution in THF (0.075 mL, 0.15 mmol) at –78 °C. The reaction mixture was stirred for 1 h at the same temperature. Then it was hydrolyzed with a saturated aqueous solution of NaHCO<sub>3</sub> (10 mL), and extracted with CH<sub>2</sub>Cl<sub>2</sub> (3 × 20 mL). The organic phase was dried with anhydrous MgSO<sub>4</sub>, and the solvent evaporated (15 Torr). The residue was purified by column chromatography (silica gel, CH<sub>2</sub>Cl<sub>2</sub>/MeOH, 96:4) to give (–)-lasubine II (**12**) (20.4 mg, 0.07 mmol, 70%) as a yellow oil; 89:11 er [HPLC (Chiralcel OD-H column, hexane/*i*-PrOH = 90/10, 1.0 mL/min, 220 nm): t<sub>minor</sub> = 8.56 min, t<sub>major</sub> = 11.61 min]; [α]<sub>D</sub><sup>20</sup> –32.4 (*c* = 0.28, MeOH) [lit.<sup>20</sup> [α]<sub>D</sub><sup>20</sup> –34.7 (*c* = 0.32, MeOH); lit.<sup>27</sup> [α]<sub>D</sub><sup>20</sup> –51.0 (*c* = 0.12, MeOH)]; R<sub>f</sub> 0.44 (CH<sub>2</sub>Cl<sub>2</sub>/MeOH, 10:1); IR ν (neat) 3340, 2932, 1516, 1464, 1261, 1142, 1026, 749 cm<sup>–1</sup>; <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 7.12 (s, 1H), 6.99–6.89 (m, 2H), 4.17–4.09 (m, 1H), 3.85 (s, 3H), 3.82 (s, 3H), 2.96 (s, 1H), 2.82 (d, *J* = 12.1 Hz, 1H), 2.26–2.07 (m, 2H),

1.95–1.27 (m, 10H);  $^{13}\text{C}\{^1\text{H}\}$  NMR (100 MHz,  $\text{CDCl}_3$ )  $\delta$  151.25 (C), 150.8 (C), 122.2 (CH), 113.8 (CH), 113.3 (CH), 65.6 (CH), 64.4 (CH), 59.8 (CH), 56.9 ( $\text{CH}_3$ ), 56.8 ( $\text{CH}_3$ ), 53.9 ( $\text{CH}_2$ ), 41.8 ( $\text{CH}_2$ ), 40.0 ( $\text{CH}_2$ ), 33.2 ( $\text{CH}_2$ ), 25.9 ( $\text{CH}_2$ ), 24.8 ( $\text{CH}_2$ ); LRMS (EI)  $m/z$  291 ( $\text{M}^+$ , 100%) 290 (34), 248 (20), 246 (30), 232 (21), 191 (26), 190 (21), 165 (36), 164 (86), 163 (11), 154 (79), 151 (22), 149 (13), 126 (26), 110 (26), 96 (17), 91 (13), 84 (23), 55 (13).

## ASSOCIATED CONTENT

**Supporting Information.** Copies of  $^1\text{H}$ ,  $^{13}\text{C}$  NMR and DEPT spectra for compounds **5b**, *ent*-**5h**, **5j**, **7**, **8**, **11** and **12**. Copies of chiral HPLC and GC chromatograms for compounds **7**, **8**, **11** and **12**.

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